REMARKS

Claims 49-50, 63-71, 77-81, 83, 88, 89, 91 and 92 are pending in the present application. A summary of the changes to the claims is as follows:

1) In claim 49, R_3 is fluoro and is located in the "meta" position with respect to R_4 and "para" with respect to –NH. Original claims 7 and 9 support these changes.
2) In claim 49, the proviso wherein R_3 and R_4 can not be nitro is deleted.
3) In claim 50, R_3 is fluoro
4) Claim 56 is deleted.
5) Claim 79 has been amended to be consistent with claim 49.
6) Claim 80 is amended to include only compounds within amended claim 49.

Unity of Invention Issues

Responsive to the Unity of Invention Requirement, the claims have been amended such that substituents R_4 and R_3 now both represent fluoro. Further, the fluoro representing R_3 is located at the "meta" position of the "C" phenyl ring.with respect to R_4 and "para" with respect to -NH. Based on these definitions, it is submitted that a structural feature common to all the compounds of formula I representing a structural contribution is achieved, which satisfies unity of invention standards and which differentiates all the compounds falling within amended claim 49 from the compounds of both Ottosen '670 (US 6,541,670) and Ottosen '744 (WO 01/05744). Applicant also respectfully maintains a traversal of the Unity of Invention Requirement to the extent that claims 83, 88, 89 and 92 have been withdrawn. The reasons in support of this traversal were submitted with the Response filed May 28, 2008 and are deemed repeated herein.

Issues under 35 USC 103(a)

Claims 49, 63-65, 67, 69-71, 77, 78, 81 and 91 have been rejected under 35 USC 103(a) as being unpatentable over Ottosen '744 (WO 2001/05744) in view of Patani et al. (Chem Rev, 1996, 3147-3176).

The above-noted rejection is traversed based on the following reasons.

Distinctions over Cited References

In support of the above obviousness rejection, the Examiner has identified Example 9, Compound 118 of Ottosen '744 and included a compound structure at top page 4 of the Office Action. However the structure includes an error in that the compounds of Ottosen '744 require an amino group (not a nitro group as shown in the Office Action) attached to the "C" phenyl ring. In formula II of Ottosen '744, the nitrogen-atom of ring C may be substituted with hydrogen, CF_3, alkyl, carbamoyl, alkoxycarbonyl or alkaloyl. The R_3-group can not be nitro.

The present claims differ in scope significantly from the compounds disclosed by Ottosen '744. First, the claimed compounds do not include an amino-group as a possible R_3 or R_4 substituent. Rather, R_3 and R_4 in the claimed compounds are both fluoro in fixed positions on ring C. Therefore, significant structural distinctions exist over Ottosen '744.

The Examiner further states that "...at the filing date it would have been obvious to a skilled person to synthesize the compound of [Ottosen '744 (not "Villhauer" as stated)] and biosterically replace a hydrogen at the 2-position of the phenyl ring with fluorine according to Patani et al. with a reasonable expectation of success." The distinctions over Ottosen '744 are noted immediately above. Patani et al. fails to disclose any compounds having the significant structural features of any of the Ottosen '744 compounds and is relied upon for the extremely broad suggestion that a fluoro group may replace a hydrogen to improve some properties. Patani et al. also suggests replacing hydrogen with other functional groups, such as hydroxyl, amino or methyl groups, and these suggested changes can be employed for a vast array of compounds having different structures.

Patani et al. cannot be combined with Ottosen '744 since there is no basis to one skilled in the art to suggest that any of the Ottosen '744 compounds would exhibit improved properties if any of the changes in Patani et al. were made. Patani et al. fails to provide any reasonably specific suggestion to make specific changes to the compound structures of any of the Ottosen '744 compounds. Additional reasons which undermine the alleged obviousness based on Patani et al. follow.

Patani et al. discloses in column 1-2, what has been known for many years, i.e. that bioisosterism represent *one* approach for the rational modification of lead compounds.

At page 3149 it is stated that "...the difference in the electronic effects (between H and F) is often the basis for major differences in the pharmacological properties of agents where fluorine has been substituted for hydrogen..." However it is not stated that replacement of hydrogen with fluorine will result in more beneficial compounds but only that major differences in pharmacological properties may be observed. A few specific examples are listed which relate to a specific enzymatic process, naphthyl-fused diazepines and steroid analogues respectively. Patani et al. is absolutely silent about fluorine vs hydrogen replacement in aminobenzophenone analogues and in particular there is no indication that a fluoro substituent in the 2-position of the C-ring of aminobenzophenone analogues would provide compounds with increased inhibitory activity.

If one skilled in the art studied Patani et al. were hypothetically inclined to try replacing a hydrogen on the C-ring of an aminobenzophenone structure, he would learn from Ottosen '670, which concern aminobenzophenone compounds similar to the present invention, that replacement of hydrogen with fluoro in the C-ring would indeed *not* provide compounds with an improved TNF-α or IL-1β inhibitory activity compared to the similar compounds without the fluoro atom being present. In fact compounds 102, 116, 130, 131 in Ottosen '670 are identical except that compounds 116, 130 and 131 have a fluoro atom in the 4, 5 and 3 position, respectively, whereas compound 102 has a hydrogen atom in this position. The skilled person comparing these compounds would find that compounds 116 and 130 indeed show a difference in the pharmacological properties compared to compound 102, but in a non-beneficial way. In fact the TNF-α or IL-1β inhibitory activity for 116 and 130 are considerably decreased compared to compound 106 and at the same level for compounds 131 and 102, see IC_{50}-values (nM) extracted from table 1 in Ottosen '670 below:

Compound:	IL-1β	TNF-α
102	13	4.0
116	2	7.9
130	40	6.3
131	13	4.0

For comparison, the compounds of the present invention show IL-1β and TNF-α inhibition concentration-values (IC_{50}) of <13 nM and <4 respectively as evidenced by the results in Table 1 in the present application as filed.

Therefore, a skilled person having reviewed Patani et al. and Ottosen '670 would indeed not be able to predict that replacing a hydrogen atom in the C-ring in a benzoaminophenone compound similar to the compounds according to the present invention would yield compounds with a considerably improved inhibitory TNF-α or IL-1β activity. Further, one skilled in the art would not have any reasonable basis to be inclined to substitute the (substituted) amino group in ring C with a fluoro group, as the (substituted) amino group constitutes an essential part of the structure of the compounds disclosed in Ottosen '744. Consequently, significant patentable distinctions exist over both Ottosen '744 and Patani et al., whether taken separately or improperly combined.

Double Patenting Issues

Claims 49, 50, 56, 58, 63-71, 77-81 and 91 have been rejected on the ground of nonstatuutory obviousness-type double panting as being unpatentable over claim 1 of Ottosen '670 (US 6,541,670). This rejection is respectfully traversed.

In response to this rejection, it is submitted that the amended claims filed with this response remove the basis for this rejection. The compounds according to the claims filed with this response are not only distinct from the claims of '670 with respect to the R_5/R_6 substituents and with respect to the fixed 2,4-difluoro-phenyl ring (ring C), these compounds also exhibit unexpectedly, advantageously improved inhibitory activity towards TNF-α or IL-1β as

compared to the compounds claimed in Ottosen '670. See comparable data in the table listed above and table 1 in the application as filed. Consequently, this rejection should be withdrawn.

It is submitted for the reasons above that the present claims define patentable subject matter such that this application should now be placed in condition for allowance.

If any questions arise in the above matters, please contact Applicant's representative, Andrew D. Meikle (Reg. No. 32,868), in the Washington Metropolitan Area at the phone number listed below.

If necessary, the Commissioner is hereby authorized in this, concurrent, and future replies to charge payment or credit any overpayment to Deposit Account No. 02-2448 for any additional fees required under 37.C.F.R. §§1.16 or 1.17; particularly, extension of time fees.

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Respectfully submitted,

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